UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,330	04/25/2005	Peter Carmeliet	50304/056001	3636

21559 7590 04/13/2007

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,330	CARMELIET ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The finality of the rejection of the last Office Action (17 October 2006) is *withdrawn* in view of the new grounds of rejection set forth below.

Status of Application, Amendments and/or Claims

The amendment filed 15 February 2007 has been entered in full. Claims 2-9, 11-13 and 18 are cancelled. Claim 14 is withdrawn. Claims 1, 10, 15-17 are under examination.

Withdrawn Objections And/Or Rejections

The rejection to claims 1, 10, 15-17 under 35 U.S.C. 103(a) as being unpatentable over Niida *et al.* (Journal of Experimental Medicine Vol. 190/2:293-298, 1999), as set forth at pages 3-5 of the previous Office Action (17 October 2006), is *withdrawn* in view of the amendment (15 February 2007).

The rejection to claims 1, 10, 11, 13, 15-18 are under 35 U.S.C. 112, first paragraph, written description (new matter), as set forth at pages 5-7 of the previous Office Action (17 October 2006), is *withdrawn* in view of the amendment (15 February 2007).

The rejection to claims 1, 10, 11, 13, 15-18 under 35 U.S.C. 112, second paragraph, as set forth at page 7 of the previous Office Action (17 October 2006), is *withdrawn* in view of the amendment (15 February 2007).

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for reducing bone resorption in an individual diagnosed to have osteoporosis, said method comprising administering **an anti-placental growth factor antibody or anti-VEGFR-1 antibody** to the individual in an amount effective to reduce bone resorption (claim 1) OR

a method for suppressing bone resorption in osteoporosis, said method comprising contacting an osteoclast cell with **an anti-placental growth factor antibody or anti-VEGFR-1 antibody** so that bone resorption is suppressed (claim 16)

does not reasonably provide enablement for:

a method for reducing bone resorption in an individual diagnosed to have osteoporosis, said method comprising administering **an antagonist of placental growth factor (or the antagonists as recited in claim 10)** to the individual in an amount effective to reduce bone resorption OR

a method for suppressing bone resorption in osteoporosis, said method comprising contacting an osteoclast cell with **an antagonist of placental growth factor** so that bone resorption is suppressed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Bone resorption is bone loss due to increased osteoclast activity. The specification teaches the examination of bone phenotype in placental growth factor (PlGF) knockout mice (Examples, page 19). The specification teaches that an increase of 18% in trabecular bone volume was measured in the proximal tibial metaphysis of newborn PlGF deficient mice compared to WT mice. The increase became more pronounced in 12 weeks-old PlGF deficient mice. The specification teaches that the total number of osteoclasts formed in bone marrow-osteoblast co-cultures of PlGF deficient mice was decrease compared to WT cultures (page 22).

The term 'antagonist of placental growth factor" encompasses a large genus. Due to limited guidance in the specification, the Examiner has interpreted the term "small molecules binding on PlGF or VEGFR-1 " (claim 10) as encompassing not only small organic molecules (page 9, line 20) but also lipids, antibodies, nucleic acids, chemical analogs, biomolecules, macromolecules, etc. "Peptides or tetrameric peptides binding on PlGF or VEGFR-1" (claim 10) can include any peptide that can bind PlGF or VEGFR-1. Further, claim 10 recites "antibodies binding on PlGF" (instead of anti-PlGF antibodies), thus this limitation encompasses any antibody which is capable of binding

PIGF. The instant specification fails to indicate that a representative number of structurally related compounds are disclosed and therefore, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claim and would not know how to make them. The specification does not address how to make and use any chemical, compound, nucleic acid, lipid, macromolecule, RNA, ribozymes, etc that would bind, affect the binding and/or signaling activity of PIGF to reduce bone resorption in an individual diagnosed to have osteoporosis.

Furthermore, the specification teaches increased bone volume in PIGF knock-out mice. It could not be predicted that the data presented in the specification would be correlative with *in vivo* treatments involving administering *any antagonist of PIGF* or the antagonists as recited in claim 10 to treat bone resorption. PIGF knock-out mice having increased bone mass is not tantamount to the administration of any PIGF antagonist to reduce/suppress bone resorption in a mammal diagnosed with osteoporosis. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Due to the large quantity of experimentation necessary to show a correlation between the bone phenotype of PIGF knock-out mice and administration of any PIGF antagonist to reduce/suppress bone resorption in an individual diagnosed with osteoporosis, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention and the breadth of the claims which fail to recite structural limitations for

peptides, antibodies and small molecules, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph, Written description

Claims 1, 10, 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is insufficient descriptive support for the genus "antagonist of placental growth factor", "peptides binding on PIGF ", "antibodies binding on PIGF", "tetrameric peptides binding on PIGF or VEGFR-1" and "small molecules binding on placental growth factor or VEGFR-1". The claimed invention is drawn to a method for reducing bone resorption in an individual diagnosed to have osteoporosis and a method for suppressing bone resorption in osteoporosis. The instant method requires the use of undisclosed antagonists of PIGF. The specification does not demonstrate possession of the instant method step, which requires the use of undisclosed compounds.

No structural characteristics of such an antagonist are provided, nor is there any indication that Applicant had possession of any antagonists. There is insufficient descriptive support for the genus. The instant claims are drawn to a genus of PIGF antagonists based entirely on function. The instant genus can encompass, lipids, antibodies, nucleic acids, chemical analogs, biomolecules, macromolecules, etc. There

is no structural element correlative with the function, nor is there any indication that Applicant is in possession of any PlGF antagonist.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed PlGF antagonist, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Because of the breadth of the claimed genus and lack of definitive structural features of the claimed genus, one skilled in the art would not recognize from the disclosure that the Applicant was in possession of the claimed genus. Applicant is

reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 10, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murakami et al. (JP 2001086982 A, translated document provided) in view of Robinson et al. (FASEB, Vol. 15, pages 1215-1217, May 2001) and Dias et al. (PNAS, Vol. 98, No. 19, pages 10857-10862, Sept. 2001).

Murakami et al. teach that the invention enables the control of formation and survival of the osteoclast by using the medicine, which adjusts activation of VEGFR-1 and to treat the illness accompanying the deviation of the bone resorption. Murakami et al. teach a method of obstructing formation of the osteoclast and bone resorption, which uses as an active ingredient the compound, which obstructs VEGFR-1 activation. Murakami et al. teach what connects with VEGFR-1 and obstructs the activation, for example, antagonist of a receptor, is the thing which obstructs the connection with VEGFR-1 and its ligand, is contained in such a compound. Murakami et al. teach that administration of an antibody with respect to the VEGRF-1 ligand obstructs the

connection of this ligand and VEGFR-1 and decreases the number of osteoclast (paragraph 0030 and Example 5). Murakami et al. teach that such illness which is the target of treatment include osteoporosis (paragraph 0031). Murakami et al. teach that when anti-VEGF antibody was administered to mice, the number of osteoclast was reduced (paragraph 0049 and Figure 4B). Murakami et al. do not teach small molecules binding on PIGF or VEGFR-1 or anti-VEGFR-1 antibodies or the administration of such.

Robinson et al. teach SU5416 (i.e. small molecule binding on VEGFR-1) as a specific antagonist to VEGFR-1. Robinson et al. teach the administration of SU5416 to mice (page 1215).

Dias et al. teach neutralizing antibodies against VEGFR-1(i.e. small molecule binding on VEGFR-1)(page 10857, 3rd paragraph and page 10858, 4th paragraph, Antibodies). Dias et al. teach the administration of neutralizing antibodies against VEGFR-1 (page 10860, last paragraph-page 10861, 2nd paragraph).

Although Murakami et al. do not teach the administration of small molecule binding on VEGFR-1 or anti-VEGFR-1 antibodies to treat osteoporosis; they propose the use of antibody anti-VEGF to inhibit osteoclasts and state that such illness which is the target of treatment include osteoporosis. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of treating osteoporosis by administering anti-VEGF antibodies as taught by Murakami et al., with a small molecules binding on VEGFR-1 (e.g. anti-VEGFR-1 antibody) with a reasonable expectation of success. The motivation and expected success is provided

by Murakami et al., who teach that obstructing formation of osteoclasts and bone resorption uses an active ingredient which obstructs VEGFR-1 activation. Murakami et al. teach what connects with VEGFR-1 and obstructs the activation, for example, antagonist of a receptor, is the thing which obstructs the connection with VEGFR-1 and its ligand are contained in such a pharmaceutical compound. It is therefor obvious for a skilled person to use the teaching of Murakami et al. to inhibit the action of VEGFR-1 on osteoclasts to include VEGFR-1 antagonists such as anti-VEGFR-1 antibodies or small molecules binding VEGFR-1. Inhibiting VEGFR-1 or VEGF is equivalent and directly obvious when it is known that VEGF acts through the VEGFR-1.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
4/5/07

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
AU1647 4/12/07